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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,989	03/03/2004	Adi Shefer	4686-121.2 US	4876

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/791,989	SHEFER ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16, 24-31, and 35-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,24-31 and 35-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-16, 24-31, and 35-44 are presently pending for examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

3. The objection to the specification regarding the use of the trademark EUDRAGIT® is withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 103

4. Claims 1-16, 24-31, and 35-44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Urquhart et al. US 4,851,231 ('231), of record in view of US 5,718,919 to Ruddy and Roy et al. US 6,475,995.

5. Applicant's arguments filed 11-10-2008 have been fully considered but they are not persuasive. Applicants traversed the instant rejection by means of pointing out the deficiencies of each reference separately. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

6. Applicants traversed the instant rejection on the grounds that "[U]rquhart et al. teach a tablet comprising particles having 100 to 2000 microns in the form of a reservoir system of tiny reservoirs. The reservoir system comprises a wall of a rate controlling

material surround the beneficial drug. The tablet containing tiny reservoirs is formed by spraying a wall material on a powdered drug to surround each drug core. Various thicknesses of the wall forming materials can be used for providing additional controlled release." Applicants further argued that, in contrast, the present claims comprise a pharmaceutical active agent incorporated by dispersion into a hydrophobic matrix into a solid nano-sphere or in both the solid nano-sphere and a microsphere. Moreover, Applicants argue that the "[m]atrix system of their invention can provide a prolonged release of an active agent from the matrix, whereas in the reservoir system, all the active will be released as soon as the coating or membrane is cracked." Applicant's arguments are not supported by any clear evidence to the contrary. Contrary to Applicant's assertions, reservoir systems of Urquhart et al. can be characterized as follows, see col. 6, lines 20-37:

> Tiny reservoirs **12** used for the purpose of this invention provide for the controlled delivery of drug **22** over a prolonged period of time. Tiny reservoirs **12** comprise a drug **23** surrounded by a wall **23** of a drug release rate controlling material that delivers drug **22** in the biological environment having a pH of greater than 3.5 to 8.0. The prolonged period of time for the purpose of this invention corresponds to the period of time reservoirs **12** are in this environment. The materials forming wall **23** are in a presently preferred proviso different materials than the materials forming matrix **21**, and they can be selected from materials that release drug **22** by different physical-chemical mechanisms in a biological environment having a pH of greater than 3.5 to 8.0. These mechanisms include erosion, diffusion, osmosis, metabolism, and the like. Wall **23** can have various thicknesses and layers as an additional aid for providing timed release of drug **22**.

7. As stated above, the materials forming both the wall comprising the reservoirs of Urquhart et al. are designed from material that delivers drug for a prolonged period of time in biological environments having a pH of greater than 3.5 to 8.0, wherein the mechanisms of drug delivery include erosion, diffusion, osmosis, metabolism and the

like. The walls can have various thicknesses and layers as an additional aid for providing time release of drug. Therefore, Applicant's description of the teachings of Urquhart et al. does not accurately reflect the teachings of the compositions of this reference. Absent evidence to the contrary, to the extent that the claims read on a controlled release composition comprising a plurality of nanospheres encapsulated in a pH sensitive microsphere, the Urquhart et al. reference in view of Ruddy et al. and Roy et al. renders the claimed invention obvious for the reasons above and those reasons below.

Furthermore, Applicants argue that both Ruddy et al. and Roy et al. "[d]o not teach or suggest a first pharmaceutical active agent incorporated by dispersion into a hydrophobic matrix forming the core of a plurality of solid-nano-spheres or incorporated into both the hydrophobic matrix of the plurality of solid nano-spheres by dispersion and the matrix material of the micro-sphere and do not cure the deficiencies of Urquhart et al." Contrary to Applicant's assertions, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "a first pharmaceutical active agent incorporated by dispersion into a hydrophobic matrix forming the core of a plurality of solid-nano-spheres or incorporated into both the hydrophobic matrix of the plurality of solid nano-spheres by dispersion and the matrix material of the micro-sphere") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With regard to claim 2, Applicants argue that none of the references teach or suggest that first active agent is incorporated in the solid nano-spheres and further comprising a second active agent encapsulated in the pH sensitive or salt sensitive matrix material wherein the pH sensitive or salt sensitive material releases the second active agent upon contact with a solution having a predetermined pH or predetermined salt concentration.

Urquhart et al. discloses a pharmaceutical delivery system comprising a plurality of nanospheres encapsulated in a pH sensitive microsphere (drawings and descriptions thereof). The microsphere is a made from a polymer matrix which keeps its physical and chemical integrity in a biological environment with a pH from 1.0 to 3.5, inclusive, and which degrades or dissolves to release the drug-laden nanospheres at a pH of 3.5 to 8.0 (col. 4, lines 9 – 29). Furthermore, Urquhart et al. provides the following description of pharmacologically beneficial substances:

In the specification and the accompanying claims the term drug denotes pharmacologically beneficial substances that are absorbed in an intestinal environment by one or more of the following transport mechanisms: active transport, passive transport, pore transport, or facilitated transport to produce a local or systemic effect in animals. The term animals as used herein includes warm-blooded mammals such as humans. The benefical drug that can be delivered in a biological environment having a pH greater than 3.5 to 8.0 are drugs that act on the central nervous system, depressants, hypnotics, sedatives, phychic energizers, tranquilizers, muscle relaxants,antiparkinson, analgesics, anti-inflammatory, hormonal, contraceptives, sympathomimetics, diuretics, antiparasites, neoplastics, hypoglycemics, electrolytes, cardiovascular, anthelmintics, and the like.

Exemplary drugs that are administered in an environment having a pH greater than 3.0 to 8 include hycanthone, aminophyline, aminosalicylic acid, chymotrypsin, sulfoxone sodium, diethylstilbestrol, erythromycin estolate, erythromycin, orenzyme, carbomycin, riboflavin, thiamine, vitamin D.sub.2, vitamin D.sub.3, vitamin B.sub.12, nitrogen mustard derivatives, phenylbutazone, acetysalicylic acid, helmintheasis xanthones, helminthiasis thioxanthones, narcotics morphine and codeine, deriviatives of phyrimedines including 5-fluorouracil and 5-brommouracil, quaternary ammonium compounds including benzomethamine, oxyphenonium, hexamethonium, and tubocurarine,

atropine, and the like. The beneficial drugs are known in the art in Pharmaceutical Sciences, by Remington, 1980, published by Mack Publishing Co.; Physicians'Desk Reference, 36 Edition, 1982, published by Medical Economics Co.; and, Medicinal Chemistry, 3rd Edition, Vol. 1 and 2, by Burger, published by Wiley-Interscience Co.

Contrary to Applicant's assertions, since the teachings of Urquhart et al. teach that a variety of pharmaceutical agents are useful in their disclosed compositions, it would have been obvious to combine one or more therapeutic agents disclosed as useful for the same purposes, for example as stated above, one or more analgesics, in a combination used for the same therapeutic purpose. See MPEP § 2144.06 which states that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted)

Absent evidence to the contrary, as stated in the prior Office Action, it would be prime facie obvious to a person of ordinary skill in the art at the time of the invention to make the formulation of '231 smaller, namely, to use nanoparticles encapsulated in a microparticle instead of microparticles encapsulated in a millimeter sized particle. The motivation comes from Ruddy, who teaches advantages of smaller sizes in drug delivery. Following the teachings of the references, the artisan would decrease the size of the millimeter sized particles of '231 proportionately with the size decrease in the microparticles, thus resulting in the instantly claimed invention. Additionally, one of ordinary skill in the art would have been motivated to modify the delivery system of Urquhart et al. to comprise a nucleic acid based drug since Roy et al. clearly teaches

the benefits of using a non-viral nanoparticulate formulation over a viral delivery system in vivo.

8. Claims 40-44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,851,231 ('231), of record, in combination with Roy et al., Ruddy and Gref et al, US 5,543,158.

Applicant's arguments filed 11-10-2008 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that since Urquhart et al. do not teach that the reservoirs contain poly(alkylene glycol) moieties on the surface, the ordinary skilled artisan would not have had reasonable expectation of success to attach antibodies to the surface of the compositions of Urquhart et al., since Gref requires the presence of poly(alkylene glycol) moieties. Applicant's arguments do not take the place of evidence. Contrary to Applicant's assertions, the prior art, including both Gref et al. Ruddy et al. teach the synthesis of nanoparticles comprising polyethylene glycol as a surface modifier. Therefore, the ordinary skilled artisan following the teachings of the cited references would have reasonable expectation of success to practice the claimed invention. As stated in the prior Office Action, it would be prime facie obvious to a person of ordinary skill in the art at the time of the invention to use attach antibodies to the nanospheres of '231 according to Gref. The motivation to do so is provided by Gref, who teaches that this manipulation allows for targeting to specific cells or organs. Since Gref teaches how to do this, the artisan would have a reasonable expectation of success. The expected result would be the drug delivery system of '231 with antibodies appended thereto according to Gref, wherein the system

was able to target specific cells or organs, and thus be delivered to a specific part of the body.

Double Patenting

9. Claims 1-16 and 24-44 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 and 25-51 of copending Application No. 10/315,801.

10. Applicants traversed the instant rejection on the grounds that since the instant rejection is provisional, Applicants are unable to respond whether the instant claims are unpatentable over the claims of the copending application. Thus the claims remain rejected until the double patenting rejection is the last outstanding rejection in the instant application, and/or Applicants file a terminal disclaimer over the copending application.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633